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Effect of feeding behavior on circadian regulation of endothelin expression in mouse colon

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ABSTRACT

Aims: The function, regulation and gene expression of the endothelin (ET) system in the intestine is not well understood. We investigated the dependence on feeding schedule and biological clock of the regulation of ET-1 gene expression in mouse colon.
Main methods: Mice were fed freely, fasted for 48 h and re-fed after fasting.
Key findings: Where indicated ET-1 gene expression was highest in the colon compared with other tissues examined in fasted mice. Fasting increased the level, while maintaining the rhythmicity, of ET-1 gene expression in epithelial colonic tissue. Re-feeding, however, decreased ET-1 gene expression and suppressed rhythmic oscillation, and the rhythmicity also changed for gene expression for circadian clocks, period-1 and period-2 (Per1 and Per2). Furthermore, the decrease in ET-1 gene expression induced by re-feeding was blocked by pre-treatment with hexamethonium and atropine. The daily change in ET-1 gene expression in colon, which depends on feeding schedule via the autonomic nervous system, is synchronized with peripheral circadian oscillators under conditions of free feeding and fasting but not re-feeding. The decrease in ET-1 gene expression in the proximal colon induced by re-feeding occurs via the nervous system.
Significance: ET-1 plays an important physiological role, which is dependent on feeding behavior.

Introduction

Endothelin (ET), mediated by two receptors, influences a variety of biological activities in many tissues including vasoconstriction, smooth muscle contraction, cell growth and cell differentiation (Yanagisawa et al., 1988; Pollock, 1998; Andrew and David, 1998; Sakurai et al., 1990; McKay et al., 1991; Wang et al., 2001; Lahav et al., 1996; Baynash et al., 1994). Localization of peptide and gene expression of the three ET isoforms and their receptors in the gastrointestinal tract of mammalian species has been reported (Takahashi et al., 1990; Yoshinaga et al., 1992; Fang et al., 1994; Bloch et al., 1991; Saida et al., 2000). However, the role of the ET system has been studied less extensively in the gastrointestinal tract than in the cardiovascular system.

Studies have suggested physiological and pharmacological actions of the ET endocrine system in the gastrointestinal tract; ET-2/vasoactive intestinal contractor (VIC) was cloned by Saida et al. (1989) and was found to be an intestinal contractor by Ishida et al. (1989). It also has been reported that ET-1 and ET-3 cause a sustained contraction mediated by the ETA and/or ETB receptors in the isolated longitudinal smooth muscle of the guinea pig ileum (Hori et al., 1994) and cecum (Okabe et al., 1995) in vitro. Furthermore, it has been reported that ET-1, ET-2/VIC, and ET-3 contribute to mucosal injury of the stomach in rat and mouse (Morales et al., 1992; Wallace et al., 1989; Kozakai et al., 2002a). In addition, it has been reported that loss of ET-3 and/or ETB receptor function may be involved in the abnormal development of neural crest-derived cells, causing Hirschsprung's disease (Puffenberger et al., 1994; Oue and Puri, 1999; Won et al., 2002). It also has been observed that ET-1 and ET-3 increase chloride secretion

Abbreviations: ET, endothelin; Per, period; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; VIC, vasoactive intestinal contractor.

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in rat (Moummi et al., 1992; Gonzalez Bosc et al., 2001) and rabbit (Roden et al., 1992) colon in vitro and that ET-1 inhibits glucose-coupled sodium absorption (Kuhn et al., 1997) and enhances bicarbonate secretion in the small intestine of rat (Takeuchi et al., 1999) in vitro. However the degree to which environmental conditions affect the regulation of ET gene expression in the gastrointestinal tract has not been demonstrated.

Feeding is an important factor influencing the physiologic action of the gastrointestinal tract in many species. To understand the regulation of ET gene expression in the gastrointestinal tract, we studied the effects of feeding and fasting on the gene expression of ET-1 and ET-2/VIC as well as their regulatory mechanisms (including the neuronal system) in mouse colon.

Materials and methods

Animal, tissue and RNA

Male ICR mice obtained from Nippon Clea (Tokyo, Japan) were housed in a temperature-controlled animal room. Lights were kept on between 0700 h and 1900 h each day to maintain 12-hour light and dark periods over a 24-hour cycle. All animals were allowed access to water and food ad libitum and were maintained under these conditions for two weeks. In the re-feeding experiments, food was removed at 1000 h for fasting and was given again at 1000 h after 48 h of fasting. The re-feeding period lasted at least 24 h. In experiments involving intravenous injection, we used the following solutions: 100 μL of hexamethonium bromide solution (a ganglionic inhibitor, 10 μg/g of body weight), atropine solution (a muscarinic inhibitor, 2 μg/g of body weight), a glucose solution (1 mg/g of body weight) and saline as a control. We used 500 μL of glucose solution (2.5 mg/g of body weight) for intragastric injection. Our experimental procedures were in accordance with the Guidelines on Handling of Laboratory Animals for our institution.

Mice (7–8 weeks old) were sacrificed by cervical dislocation. Excised tongue, stomach, duodenum, jejunum, proximal colon and pancreas were washed with ice-cold PBS. These tissues were used for gene expression analysis. Total RNAs were prepared from excised tissues using a commercial kit (Isogen solution; Nippon Gene, Japan).

Real-time polymerase chain reaction (PCR) for ET-1 and ET-2/VIC

The method used has been described previously (Kozakai et al., 2002b). Sample cDNA for real-time PCR was obtained by reverse transcriptase reaction of total RNA. Amplification was carried out by two-step PCR using the TaqMan PCR kit (PE Applied Biosystems, USA). Oligonucleotide primers for murine ET-1 (GenBank accession no. D43775) were 5′-TTCCCGTGATCTTCTCTCTGCT-3′ (sense) and 5′-TCTGCTTGGC-AGAAATTCCA-3′ (antisense). Oligonucleotide primers for murine ET-2/VIC (GenBank accession no. NM_007902) were 5′-CTGCGTTTTCGTCGTTGCT-3′ (sense) and 5′-TGCAGCTCATGGTGTTAT CTCTTC-3′ (antisense). Oligonucleotide primers for murine GAPDH (GenBank accession no. BC096440) were 5′-CTTCACCACCATGGAGAA GGC-3′ (sense) and 5′-GGCAT-GGACTGTGGTCATGAG-3′ (antisense). The detection probes (TaqMan Probe, PE Applied Biosystems, USA) for murine ET-1, ET-2/VIC and GAPDH were FAM-ACAAGGAGTGTG TCTACTTCTGCCAC-CTGG-TAMRA, FAM-CTGCAACTCCTGGCTTGACAAG GAA-TAMRA and FAM-CCTGGCCAAGGTCATCCATGACAACTTT-TAMRA, respectively. Reaction conditions were 95 °C for 10 min followed by 50 cycles of the amplification step (95 °C for 20 s and 62 °C for 2 min). The amplification products from mRNAs were predicted to be 370, 422 and 238 base pairs (bp) for ET-1, ET-2/VIC and GAPDH, respectively. The gene expression rate was obtained by normalizing the amount of ET-1 or ET-2/VIC with that of GAPDH using the following formula:

[amount of ET-1 or ET-2/VIC cDNA in a sample / amount of GAPDH cDNA in a sample] × 100.

Northern blot analysis for period-1 (Per1) and period-2 (Per2)

The method used was the same as that described by Oishi et al. (2002). Total RNA was separated on a 1% agarose/0.7 M formaldehyde gel. Each lane contained 20 μg of total RNA from one tissue. RNA was transferred to a nylon membrane (GeneScreen Plus, DuPont, USA) by passive capillary transfer and probed with ^{32}P-labeled random primed probes. Probes were hybridized to blots at 55 °C, and the final wash was carried out at 55 °C in 0.1 × SSPE/1% sodium dodecyl sulfate for 40 min. Hybridized blots were imaged and analyzed by a BAS 2000 Bio-Imaging Analyzer (Fuji Photo Film, Tokyo, Japan). Hybridization signal of period-1 (Per1) messenger RNA (mRNA) and period-2 (Per2) mRNA was normalized by the amount of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA, as described previously (Oishi et al., 2002; Hanai et al., 2005; Sakamoto et al., 1998). The cDNA hybridization probes were generated from cDNA fragments of rat Per1 (bases: 2358–3114; GenBank accession no. XM_340822), rat Per2 (bases: 1123–1830; GenBank accession no. AB016532) and rat GAPDH (GenBank accession no. X02231), because the sequences of the cDNA fragments are almost the same in rat and mouse.

Statistical analysis

The results are represented as the mean + SEM (mean ± SEM). The mean values were analyzed by Student's *t*-test or one-way analysis of variance (ANOVA) followed by Bonferroni's multiple range test, except for experiments involving intravenous injection. For the intravenous injection experiments, Welch's *t*-test was used because variant values were different among all groups (Zer, 1984). P values of less than 0.05 were considered statistically significant.

Results

The effect of fasting and re-feeding on the gene expression of ET-1 and ET-2/VIC

We studied the effect of fasting for 48 h followed by re-feeding on the gene expression of ET-1 and ET-2/VIC in the tongue, stomach, duodenum, jejunum, proximal colon and pancreas of mouse ($n = 3$). Both ET-1 and ET-2/VIC genes were expressed in the tongue, stomach, duodenum, jejunum, proximal colon and pancreas of freely fed mice (Figs. 1 and 2). In these mice the highest ET-1 level was observed in the pancreas (2.23 + 1.24, Fig. 1). The 48-hour fast increased ET-1 gene expression, and this increase was most significant in the proximal colon and duodenum in comparison with the other tissues (proximal colon: 3.86 + 1.1, duodenum: 0.06 + 0.01, $P < 0.05$). Re-feeding for 0.5 or 2.0 h after the 48-hour fast decreased the fast-induced ET-1 gene expression rates to the same levels as those found in freely fed mice in all tissues examined except the pancreas.

In contrast, the highest level of expression for ET-2/VIC was observed in the jejunum (0.64 + 0.08) of freely fed mice. However fasting and re-feeding did not cause significant change in ET-2/VIC gene expression in any of the tissues examined (Fig. 2).

We chose, therefore, to investigate in detail the mechanism by which fasting and re-feeding affect the regulation of ET-1 gene expression. Based on the observation that proximal colon is the site exhibiting the greatest response of ET-1 gene expression to the 48-hour fast, we used tissue from the colon for these additional studies.

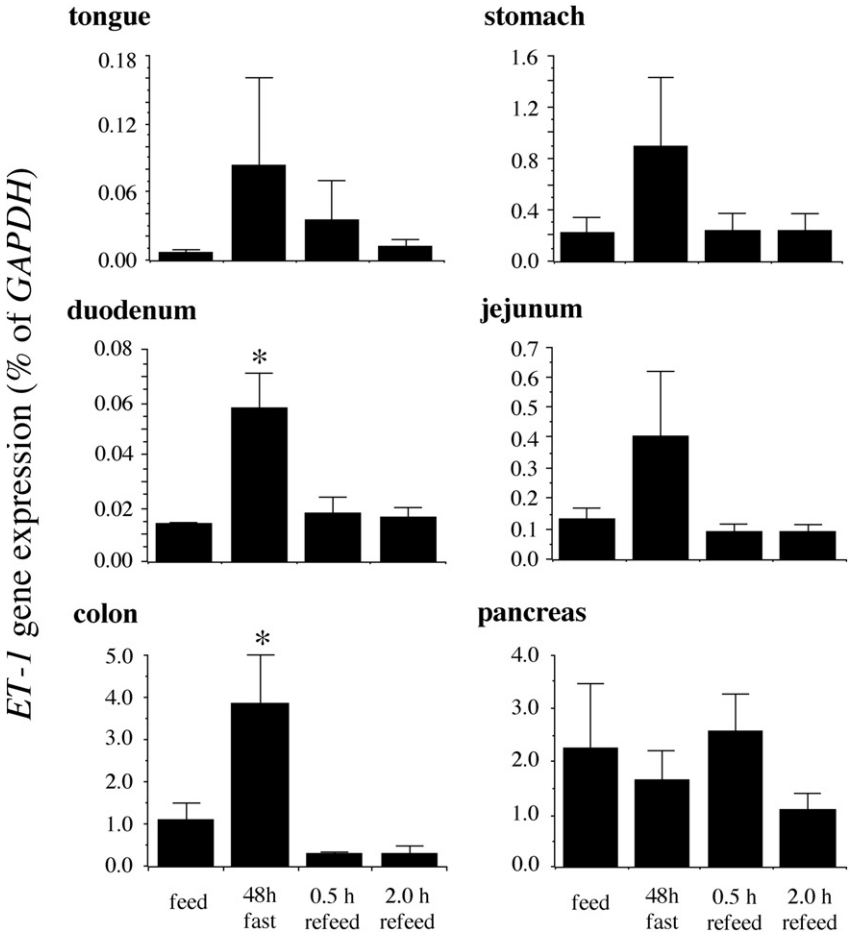

Fig. 1. The effects of fasting and re-feeding on ET-1 gene expression in mouse tongue, stomach, duodenum, jejunum, colon and pancreas. Mice were allowed to feed ad lib (free). After a fasting period of 48 h (fast), mice were able to re-feed for 0.5 or 2.0 h (0.5 h re-feed and 2.0 h re-feed). Gene expression levels were measured by real-time PCR and calculated by normalizing the expression level of ET-1 with that of GAPDH. Results are shown as the mean + SEM (n = 3). Asterisks represent a significant difference from the other treatment groups in the duodenum and colon ($P < 0.05$; Bonferroni's test).

Effects of fasting and re-feeding on circadian gene expression of ET-1, Per1 and Per2

We observed that in the colon of freely fed mice ET-1 expression rises and falls in a rhythmic manner with an approximately 24-hour period (Fig. 3A). Fasting increased the amplitude of ET-1 expression, while the 24-hour rhythmic period remained unchanged. Re-feeding caused a dramatic decrease in ET-1 expression and inhibited the rhythmicity of ET-1 expression for at least 24 h after re-feeding (Fig. 3A).

Under the same conditions, we also measured the expression of Per1 and Per2, genes that govern the molecular mechanisms controlling the circadian clock in mammals and which exhibit oscillatory expression in a circadian pattern in other tissues as described in earlier studies (Hoogerwerf, 2010; Malloy et al., 2012; Hoogerwerf et al., 2010; Balakrishnan et al., 2012; Stow et al., 2012; Wu et al., 2012). As shown in Fig. 3B and C, Per1 and Per2 gene expression in the colon tissue exhibited circadian oscillation during fasting. After re-feeding Per1 gene expression displayed a slightly altered circadian oscillation, while Per2 gene expression was temporarily increased and the rhythm was disrupted (Fig. 3C).

Autonomic nervous system involvement in ET-1 gene expression in the colon

To identify the pathway mediating the decrease in the ET-1 gene expression in the proximal colon induced by re-feeding, we examined the effects of the intragastric and intravenous injection of glucose solution. Results (% of values in non-injected) are shown as the mean + SEM (n = 3). As shown in Fig. 4A, the intragastric administration of glucose to 48-hour fasted mice resulted in significantly decreased ET-1 gene expression as compared to non-injected, fasted mice (100.0 + 5.6 vs. 67.2 + 2.5, $P < 0.05$). However, intravenous injection of glucose did not affect ET-1 gene expression (100.0 + 5.6 vs. 102.3 + 8.7).

To investigate whether or not the autonomic nervous system is involved in mediating the decrease in ET-1 gene expression in the colon of re-fed mice, we measured ET-1 gene expression in the proximal colon of the mice with a neuronal blocker, hexamethonium (ganglionic inhibitor) or atropine (muscarinic inhibitor), administered intravenously 15 min before re-feeding. Results (% of values in non-injected mice) are shown as the mean + SEM (n = 3). As shown in Fig. 4B, treatment with hexamethonium or atropine blocked the decrease in the ET-1 gene expression that occurs upon re-feeding (saline: 6.6 + 1.2; hexamethonium: 113.4 + 41.7; atropine: 113.7 + 43.1).

Discussion

We carried out these experiments to understand whether feeding and fasting influence the daily periodic gene expression of ET-1 and ET-2/VIC and to determine the regulatory mechanisms mediating these rhythmic patterns in mouse colon. After 48 h of fasting, ET-1 gene expression in the tongue and gastrointestinal tract increased significantly, but ET-2/VIC gene expression was unchanged (Figs. 1 and 2). These results suggest that ET-1 and ET-2/VIC have different functions in the gastrointestinal

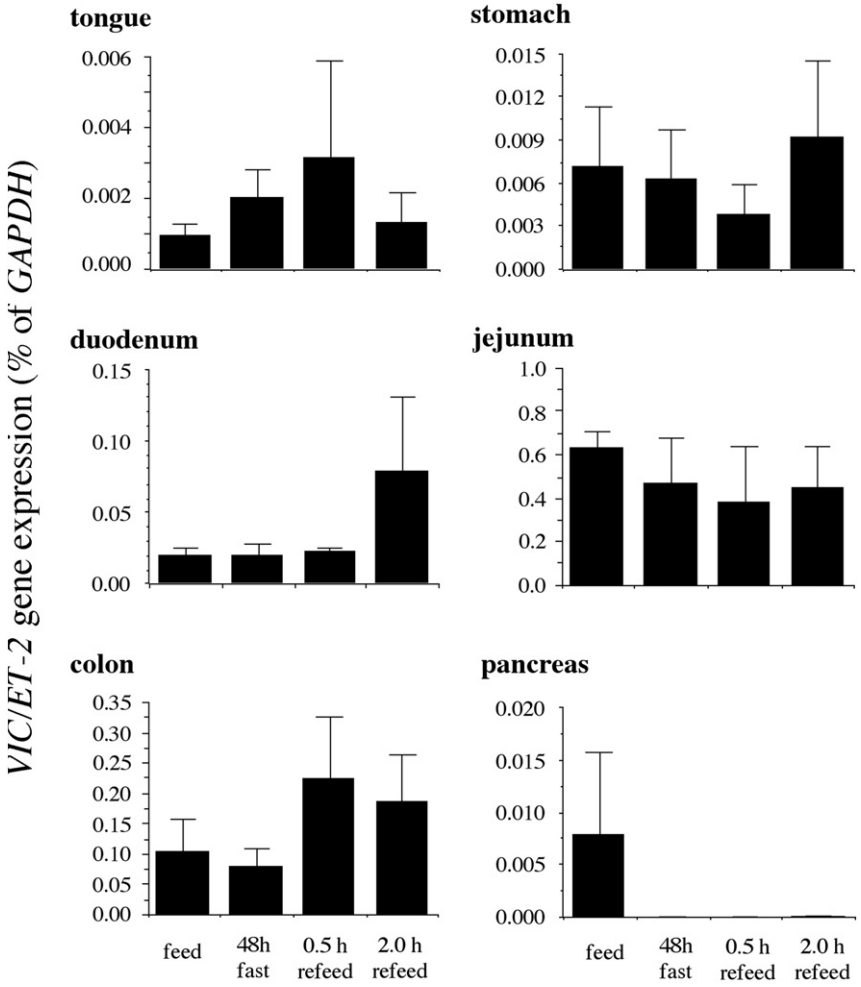

Fig. 2. The effects of fasting and re-feeding on ET-2/VIC gene expression under the same feeding conditions as described in Fig. 1. Gene expression levels were measured by real-time PCR and calculated by normalizing the level of ET-2/VIC with that of GAPDH. Results are shown as the mean + SEM (n = 3).

tract of fasted mice. It has been reported that the regulation of ET-2/VIC gene expression operates under a different mechanism than does the regulation of ET-1 gene expression in mouse antepartum uterus, pituitary and brain (Uchide et al., 1999; Masuo et al., 2003). ET-1 and ET-2/VIC gene expression might be regulated by different mechanisms under different conditions for different tissue or cell types.

To investigate the effects of fasting on ET-1 gene expression in mouse we targeted the colon because it was the tissue showing the highest level of ET-1 gene expression among the digestive system tissues tested. A significant increase in ET-1 gene expression and ET-1 peptide production induced by 48 h of fasting was observed in the colon (Fig. 1). It has been reported that the immunoreactive ET-1 peptide is localized in the epithelial tissue of the small intestine and colon in many species (Takahashi et al., 1990; Inagaki et al., 1992; Nankervis et al., 2000; Inagaki et al., 1991). However, these reports did not address the relationship between ET-1 expression in the gastrointestinal tract and feeding behavior. We have shown here for the first time that regulation and function of ET-1 in the epithelial tissue of the colon do depend on feeding behavior.

We found that in freely fed mice ET-1 gene expression is high under daylight conditions and low in conditions of darkness during a 24-hour period (Fig. 3A). However, re-feeding decreased ET-1 gene expression under daylight conditions. Contrary to normal nocturnal feeding behavior, re-fed mice feed in daylight (Fig. 3A). These observations indicate that ET-1 gene expression is influenced by feeding behavior. Because ET-1 induces contraction of blood vessels, a decrease in ET-1 upon feeding might increase absorbed nutrient-containing blood flow from intestine to liver. Low ET-1 gene expression and peptide concentration also might delay passage of digesta and increase absorption of nutrients from digesta because ET-1 increases active Cl^- secretion (Kozakai et al., 2008) and colonic subepithelial myofibroblast contraction (Egidy et al., 2000; Nankervis and Nowicki, 2000; Kernochan et al., 2002). Furthermore, low ET-1 expression could inhibit glucose absorption (Takeuchi et al., 1999) in the intestinal tract.

Re-feeding led to a decrease in ET-1 gene expression in the colon after 0.5 h (Fig. 1, Fig. 3A, and Fig. 4B). In addition, the increase in ET-1 gene expression induced by fasting was mitigated when glucose solution was administered intragastrically, but not when administered intravenously (Fig. 4A). As shown in Fig. 4B, the decrease in ET-1 gene expression observed upon re-feeding was blocked by pre-treatment with hexamethonium or atropine. These results suggest that the decrease in ET-1 gene expression in the proximal colon induced by re-feeding occurs via the nervous system, probably as a result of the activation of mechanoreceptors by the inflow of food or liquid to the stomach.

It is understood that biological clocks are important to the digestive system (Scheving, 2000). An 8-hour variation of circulating ET-1 concentration in humans has been reported (Herold et al., 1998). Also, the differential circadian expression of ET-1 gene has been reported in the rat suprachiasmatic nucleus, brain, heart and lung (Hanai et al., 2005). It is understood that the three period proteins (Per1, Per2 and Per3) are important components of the circadian oscillator that regulates the biological clock in the mammalian hypothalamic suprachiasmatic nucleus (SCN) (Ishida et al., 1999; Zylka et al., 1998) and peripheral tissue (Oishi et al., 2002; Balsalobre et al., 1998; Sakamoto et al., 1998). Therefore it is thought that the biological clock in the SCN might regulate period

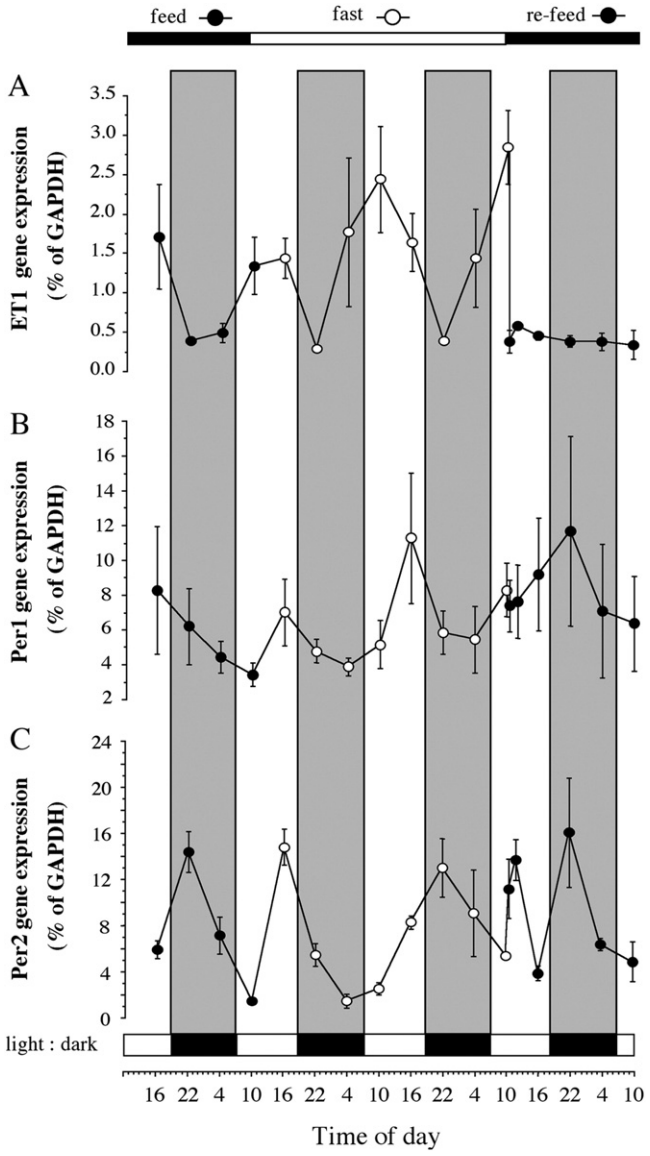

Fig. 3. The daily oscillation of ET-1 (A), Per1 (B) and Per2 (C) gene expression levels in the colon of mice fed ad lib, fasted for 48 h and re-fed for 24 h. ET-1 and period gene expression levels were measured with real-time PCR (A) and Northern blot (B and C) methods, respectively. Both expression levels were calculated by normalizing with GAPDH. Results are shown as the mean ± SEM (n = 3). Open and shaded bars indicate light and dark conditions, respectively. Closed circles indicate ad lib feeding. Open circles indicate fasting conditions.

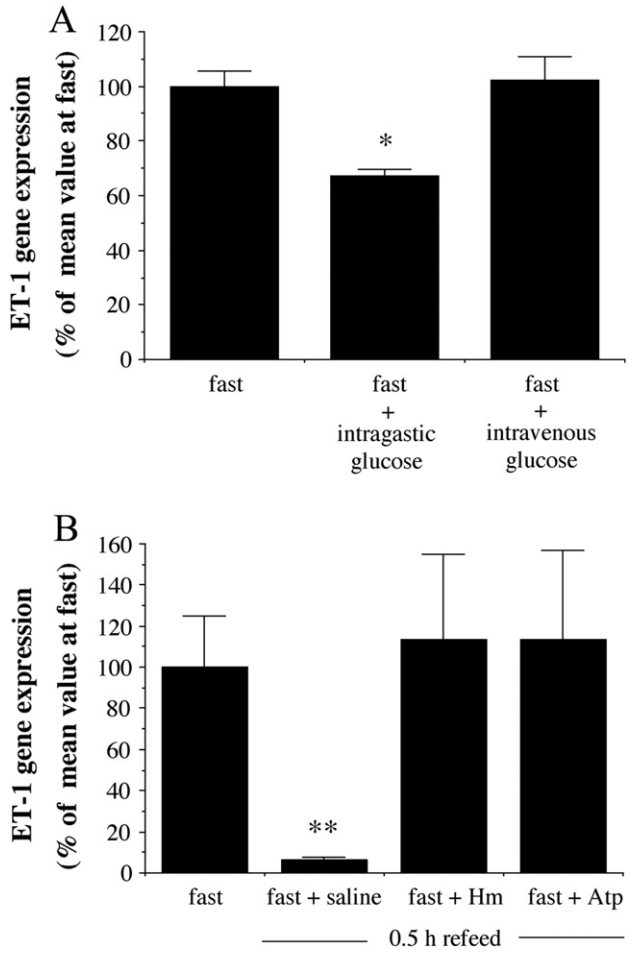

Fig. 4. Autonomic nervous system regulates ET-1 gene expression induced by fasting and re-feeding. A: Effects of intragastric (500 μL) and intravenous (100 μL) glucose injection on ET-1 gene expression in the colon of mice fasted for 48 h. Gene expression in the colon 30 min after glucose injection was measured by real-time PCR and calculated by normalizing the expression level of ET-1 with that of GAPDH. Results (% of values in non-injected mice after a 48-hour fasting) are shown as the mean + SEM (n = 3). Asterisks represent a significant difference from the other treatment groups ($P < 0.05$; Bonferroni's test). B: Pretreatment with hexamethonium bromide (Hm; 1 mg/100 g body weight) or atropine (Atp; 200 μg/100 g body weight) at 30 min before re-feeding suppresses the decrease in ET-1 gene expression in the mouse colon induced by re-feeding after a 48-hour fast. A saline solution (100 μL) was used as a control. Gene expression levels were measured by real-time PCR and calculated by normalizing the expression level of ET-1 with that of GAPDH. Results (% of values in non-injected mice before 15 min of re-feeding) are shown as the mean + SEM (n = 3). Asterisks represent a significant difference from fasted mice ($P < 0.01$; Welch's *t*-test).

proteins in the colon, and the period proteins in the colon might regulate the rhythmicity of the digestive system. ET-1 stimulates *Per1* clock gene expression in a Rat-1 cell line, suggesting a relationship between ET1 and the period clock gene in the SCN and peripheral tissue (Yagita et al., 2001). In our study, fasting increased the level of *ET-1* gene expression in the epithelial colon while maintaining the same oscillatory period, and re-feeding eliminated the rhythmicity of ET-1 gene expression (Fig. 3A). This result suggests that ET-1 gene expression might be regulated by the biological clock under free-feeding and fasting conditions, as rhythmic expression of Per1 and Per2 has been observed in the colon (Fig. 3B, C). In contrast, ET-1 gene expression might be regulated by the neuronal system, independent of the biological clock, under re-feeding conditions. After re-feeding, Per1 gene expression showed a slightly altered circadian oscillation, while Per2 gene expression was temporarily increased and the rhythm was disrupted (Fig. 3B, C). After re-feeding, the phase angle of Per1 and Per2 did not recover (Fig. 3B, C), suggesting that Per1 and Per2 mRNA oscillations were not restored. This disarrangement might be due to the vulnerability of Per1 and Per2 mRNA expression to perturbation. To gain a better understanding of this phenomenon, we plan to repeat the experiments, extending the duration of the re-feeding regime to the point at which expression levels of ET-1, Per1, and Per2 return to normal. To determine whether Per1 and Per2 mRNA expression levels are particularly vulnerable to interrupted feeding, we plan in a future study to more closely examine the relationship between ET-1 gene expression and circadian rhythm by examining additional oscillating genes that exhibit a diurnal rhythm with phase angles that differ from those of Per1 and Per2. It was previously reported that ET-1 expression is dependent on Per genes in the kidney (Stow et al., 2012) and Per gene expression levels changed after re-feeding in the heart and kidney (Wu et al., 2012). Our experiments did not reveal the mechanism for the loss of rhythmicity of ET-1 gene expression after re-feeding. Our experiments also did not elucidate the dependence of ET-1 expression on clock genes, Per1 and Per2; we will explore this dependence further in experiments using clock gene deficient mice. Further analyses using endothelin receptor genes and other clock genes such as

Cry1/2, Bmal1, Dbp, Rev-erb, and Ror are also important for understanding these interrelationships.

Conclusion

In conclusion, ET-1 plays an important physiological role, which is dependent on feeding behavior.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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